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APPLICATION NUMBER	FILING DATE	FIRST NAMED APPLICANT	ATTY. DOCKET NO.
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EXAMINER

HM32/0902

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ART UNIT	PAPER NUMBER
1641	6

DATE MAILED: 09/02/98

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

OFFICE ACTION SUMMARY

☒ Responsive to communication(s) filed on 6/11/98.

☒ This action is **FINAL**.

☐ Since this application is in condition for allowance except for formal matters, **prosecution as to the merits is closed** in accordance with the practice under *Ex parte Quayle*, 1935 D.C. 11; 453 O.G. 213.

A shortened statutory period for response to this action is set to expire 3 month(s), or thirty days, whichever is longer, from the mailing date of this communication. Failure to respond within the period for response will cause the application to become abandoned. (35 U.S.C. § 133). Extensions of time may be obtained under the provisions of 37 CFR 1.136(a).

Disposition of Claims

☒ Claim(s) 1-9 is/are pending in the application.
Of the above, claim(s) _____ is/are withdrawn from consideration.
☐ Claim(s) _____ is/are allowed.
☒ Claim(s) 1-9 is/are rejected.
☐ Claim(s) _____ is/are objected to.
☐ Claim(s) _____ are subject to restriction or election requirement.

Application Papers

☐ See the attached Notice of Draftsperson's Patent Drawing Review, PTO-948.
☒ The drawing(s) filed on _____ is/are objected to by the Examiner.
☐ The proposed drawing correction, filed on _____ is ☐ approved ☐ disapproved.
☐ The specification is objected to by the Examiner.
☐ The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. § 119

☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d).

☐ All ☒ Some* ☐ None of the CERTIFIED copies of the priority documents have been

☐ received.
☐ received in Application No. (Series Code/Serial Number) _____.
☐ received in this national stage application from the International Bureau (PCT Rule 17.2(a)).

*Certified copies not received: _____.

☒ Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e).

Attachment(s)

☒ Notice of Reference Cited, PTO-892
☐ Information Disclosure Statement(s), PTO-1449, Paper No(s). _____
☐ Interview Summary, PTO-413
☒ Notice of Draftperson's Patent Drawing Review, PTO-948
☐ Notice of Informal Patent Application, PTO-152

--SEE OFFICE ACTION ON THE FOLLOWING PAGES--

U.S. GPO: 1998-404-496/40517

CHANGE IN ART UNIT

The Group and/or Art Unit location of your application in the PTO has changed. To aid in correlating any papers for this application, all further correspondence regarding this application should be directed to Group Art Unit **1641**.

AMENDMENT ENTRY

The **AMENDMENTS AND REMARKS** filed June 11, 1998 (paper no. 5) is acknowledged and has been entered. Claims 1, 2 and 4-6 have been amended. Claim 9 has been added. Claims 1-9 are pending.

PRIOR CITATION OF TITLE 35 SECTIONS

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

DRAWINGS

The drawings are objected to for reasons of record (see PTO-948 attached to paper no. 4). Correction is required. However, formal correction of the noted defect can be deferred until the application is allowed by the examiner.

The drawings are objected to under 37 CFR 1.83(a) because they fail to show character "2" as described in the specification on page 45, line 15. Any structural detail that is essential for a proper understanding of the disclosed invention should be shown in the drawing. MPEP § 608.02(d). Correction is required.

INFORMATION ON HOW TO EFFECT DRAWING CHANGES

1. **Correction of Informalities** -- 37 CFR 1.85; 1097 O.G. 36

New formal drawings must be filed with the changes incorporated therein. The art unit number, application number (including series code) and number of drawing sheets should be written on the reverse side of the drawings. Applicant may delay filing of the new drawings until receipt of the "Notice of Allowability" (PTOL-37 or PTO-37). If delayed, the new drawings **MUST** be filed within the **THREE MONTH** shortened statutory period set for reply in the "Notice of Allowability" to avoid extension of time fees. Extensions of time may be obtained under the provisions of 37 CFR 1.136(a) for filing the corrected drawings (but not for payment of the issue fee). The drawings should be filed as a separate paper with a transmittal letter addressed to the Official Draftsperson.

2. **Corrections other than Informalities Noted by Draftsperson on form PTO-948.**

All changes to the drawings, other than informalities noted by the Draftsperson, **MUST** be made in the same manner as above except that, normally, a highlighted (preferably red ink) sketch of the changes to be incorporated into the new drawings **MUST** be approved by the examiner before the application will be allowed. No changes will be permitted to be made, other than correction of informalities, unless the examiner has approved the proposed changes.

Timing of Corrections

Applicant is required to submit acceptable corrected drawings within the three month shortened statutory period set in the "Notice of Allowability" (PTO-37). Within that three month period, two weeks should be allowed for review of the new drawings by the Office. If a correction is determined to be unacceptable by the Office, applicant must arrange to have an acceptable correction re-submitted within the original three month period to avoid the necessity of obtaining an extension of time with extension fees. Therefore, applicant should file corrected drawings as soon as possible.

Failure to take corrective action within the set (or extended) period will result in **ABANDONMENT** of the application.

INFORMALITIES

The disclosure is objected to because of the following informalities:

on page 59, line 19 define "zwittergent 3-12" and delete the newly inserted " [definition of zwittergent 3-12] ".

There are no detailed descriptions of Figures 5, 6, 7, 8(a)-8(c) and 9(a)-9(c). Applicant asserts that the "Brief" description of the drawings on pages 43-44 of the specification are sufficient. It is respectfully submitted that the "Brief" description of the drawings and a description of the drawings in the "Detailed" description of the invention are separate and distinct. It has been the Examiner's experience that the printer will return application files which do not contain separate "brief" and "detailed" descriptions of the drawings. Therefore, applicant is requested to insert the language of the "Brief" description of Figures 5, 6, 7, 8(a)-8(c) and 9(a)-9(c) at an appropriate cite in the specification after page 45 to obviate this issue. Applicant is thanked in advance for his cooperation.

Appropriate correction is required.

NON-ART BASED REJECTIONS

Claims 1-9 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claims 1-9 fail to recite clear, distinct and positive method steps; contain a number of antecedent basis problems; confusing inconsistent terminology; and, implied limitations. Therefore, the following language, or its equivalent, is suggested for applicant's consideration.

1. A method for determining the presence or absence of Streptococcus Group A antigen in a sample, comprising:

(a) providing a lateral flow immunochromatographic device comprising a sample receiving region of porous material in liquid flow contact with a separate detection region of porous material,

wherein said detection region comprises a liquid mobilizable labeling reagent at a discrete labeling situs and an immobilized capture reagent at a discrete capture situs, and

wherein said labeling reagent is a detectable label coupled to a binder which specifically binds to said antigen to form a labeled complex and said capture reagent is a binder which specifically binds to said antigen or to said labeled complex;

(b) extracting said antigen from said sample with a liquid extraction solution comprising one or two extraction reagents in an assay chamber, wherein said two extraction reagents are added to said assay chamber in any order, to form a liquid extract;

(c) contacting said sample receiving region with said liquid extract whereby said liquid extract flows through said labeling situs and then through said capture situs, without further addition of reagents or manipulation of said sample; and

(d) determining the presence or absence of said antigen in said sample by detecting the presence or absence of said detectable label at said capture situs.

2. The method of claim 1 wherein said detection region further comprises both a discrete control labeling situs comprising a liquid mobilizable labeled control reagent and a discrete control capture situs comprising an immobilized control capture reagent which specifically binds to and immobilizes said labeled control reagent, and

wherein said method further comprises

(e) determining the presence of said immobilized labeled control reagent at said control capture situs as an internal control that the assay was performed properly.

3. The method of claim 1 wherein said sample is a throat swab sample and said extracting step further comprises vigorously mixing said throat swab in said extraction reagent for at least 10 seconds.

4. The method of claim 1 wherein said extraction solution comprises a 0.2-5 M sodium nitrite solution and a 0.02-2 M acetic acid solution.

5. The method of claim 4 wherein the sodium nitrite solution comprises 2 M sodium nitrite and a pH color indicator reagent and the acetic acid acid solution has a concentration of 0.3 M, wherein the 0.3 M acetic acid solution is added to the 2M sodium nitrite solution, and wherein said pH color indicator reagent changes color as the 0.3 M acetic acid solution is added to the 2 M sodium nitrite solution.

6. The method of claim 1 wherein said sample receiving region further comprises a buffer which neutralizes said liquid extract.

7. The method of claim 1 wherein one lateral flow side of said lateral flow immunochromatographic device is laminated to a backing support strip and the remaining side is not covered.

8. The method of claim 1 wherein one lateral flow side of said lateral flow immunochromatographic device is laminated to a backing support strip and the remaining side is partially covered with a plastic material which allows the capture situs to be visible and so as to leave a portion of said sample receiving region exposed for contacting said liquid extract.

9. A method for determining the presence or absence of Streptococcus antigen in a sample, comprising:

(a) providing a lateral flow immunochromatographic device comprising a sample receiving region of porous material in liquid flow contact with a separate detection region of porous material,

wherein said detection region comprises a liquid mobilizable labeling reagent at a discrete labeling situs and an immobilized capture reagent at a discrete capture situs, and

wherein said labeling reagent is a detectable label coupled to a binder which specifically binds to said antigen to form a labeled complex and said capture reagent is a binder which specifically binds to said antigen or to said labeled complex;

(b) extracting said antigen from said sample with a liquid extraction solution comprising one or two extraction reagents in an assay chamber, wherein said two extraction reagents are added to said assay chamber in any order, to form a liquid extract;

(c) contacting said sample receiving region with said liquid extract whereby said liquid extract flows through said labeling situs and then through said

capture situs, without further addition of reagents or manipulation of said sample; and

(d) determining the presence or absence of said antigen in said sample by detecting the presence or absence of said detectable label at said capture situs.

ART BASED REJECTIONS

Claims 1, 2, 4, and 6-9 are rejected under 35 U.S.C. 102(b) as being clearly anticipated by Imrich et al. (US 5,415,994).

Imrich et al. describes a lateral flow medical diagnostic assay device with extraction means.

> The devices generally comprise an extraction chamber; a labelling zone having a means for specifically labelling the analyte; and a matrix defining an axial flow path in fluid communication with the extraction chamber, which matrix comprises a sample receiving zone and capture zone located downstream from the sample receiving zone. The methods of detecting such analytes generally comprise inserting a swab containing the sample in the extraction chamber of the device as described above; inserting an extraction solution into the extraction chamber; observing accumulation of label in the capture zone of the device; and determining therefrom the presence or absence of the analyte in the sample. Kits comprising a device as described above and an extraction solution are also provided. (col. 2, lines 26-40)

For example, immunological detection of Group A streptococcus pretreats a swab containing a sample of pharyngeal exudate with nitrous acid, to expose Group A specific antigens (col. 4, lines 14-19). Fluid from the extraction chamber contacts the matrix at the sample receiving zone, which zone may contain a neutralizing agent which will neutralize the extraction solution prior to the assay (col. 5,l ines 1-8). As the treated sample flows through the labelling zone, the target analyte binds labelled antibody and continues to flow into the capture zone where the presence of analyte may be determined by visual identification of label retention in the capture zone (col. 5,l

ines 39-52). The capture zone may include a procedural control line (col. 5,l ines 53-60). Conventionally, the matrix (test strip) is contained within a solid casing (plastic housing) (col. 7, lines 11-49). The extraction solution may be contained in a single chamber vial or multi-chamber allet, which separately contains components of an unstable reaction solution. Upon mixing in the extraction chamber, the solution is activated and treats the sample. For example, nitrous acid is a relatively unstable solution. Consequently, reagents used to generate the nitrous acid, i.e. sodium nitrite and acetic acid, are mixed immediately before initiation of the antigen extraction system (col. 8, lines 50-63). The examples (beginning at col. 10, line 10) explicitly describe detection of Group A streptococcus by means of a lateral flow assay using a nitrous acid extraction solution made of equal volumes of 1 M sodium nitrite and 1 M acetic acid.

Traversal and Response

Applicant maintains Imrich et al. is not anticipatory because Imrich et al. contains no suggestion of introducing the device into extraction reagent mixture containing the extracted antigen **after the extraction has taken place**, without further manipulation of the sample. Moreover, Imrich et al. fails to teach use of a test strip without a housing as required by claim 7.

As stated in the paragraph bridging cols. 3-4, Imrich et al. teach the extraction chamber has an exit port through which the **treated** sample may flow to the sample receiving zone on the matrix. This clearly implies that the contact occurs after the extraction has taken place since Imrich et al. explicitly characterizes the sample has being **treated**. Again at col. 5, lines 1-2,

Imrich et al. state it is **the fluid from the extraction chamber** that contacts the matrix at the sample receiving zone. Similarly, at col. 9, lines 8-21, Imrich et al. states

> Refering now to the Figures, FIG. 2A and 2B illustrate one embodiment of an extraction chamber **10** has a proximal bowl **12** and a distal cylindrical portion **14**. The bowl **12** is joined to the cylindrical portion **14** by a circular opening **18**. Samples on swabs are inserted into the cylindrical portion **14** through the bowl **12**. After the sample-containing swab has been placed in the extraction chamber **10**, the extraction solution may be added to the bowl **12** and then flow into cylindrical portion **14**. The ***treated sample may be then flow through an exit port*** **16** located distally. The exit port **16** is located over the sample receiving zone of a matrix. (italicized emphasis added)

And again at col. 9, lines 47-49, Imrich et al. state "**Following analyte extraction,** the sample flows through the exit port **16** to the sample receiving zone **30** on the matrix." (emphasis added) Therefore, the argument that Imrich et al. contains no suggestion of introducing the device into extraction reagent mixture containing the extracted antigen **after the extraction has taken place**, without further manipulation of the sample is NOT persuasive. Indeed, Bogart et al. discussed *infra* suggests the time frame for a standard nitrous acid extraction is instantaneous to 30 minutes.

As to the second argument, Imrich et al. does not **require** the test matrix to be contained within a single solid housing, although this is a preferred embodiment (see col. 7, lines 11-12, "**Conveniently**, the matrix is contained within a single casing.) What Imrich et al. does require is the extraction chamber and the matrix. As described in col. 11, lines 6-31, addition of the top plate, i.e. the plastic housing, is a separate manufacturing step, the test strip having already been placed in contact with the exit orifice of the extraction chamber. Therefore, this argument is not persuasive.

Rejection II

Claims 3 and 5 are rejected under 35 U.S.C. 103(a) as being unpatentable over Imrich et al. (US 5,415,994) taken in view of Bogart et al. (US 5,494,801) and Murray (US 3,957,436).

Imrich et al. has been described *supra* and differs in failing to disclose (a) vigorous mixing of the swab and extraction reaget for at least 10 seconds; and (b) an extraction solution wherein addition of 0.3 M acetic acid to a color-indicator spiked 2 M sodium nitrite solution changes the color of the final extraction solution.

Bogart et al. defines "the standard nitrous acid extraction method" as

> a mixture of 120 µl of 0.25 M acetic acid and 100 µl of 2.3 M sodium nitrite (previously dried into the extraction tube) is used to generate nitrous acid. The acetic acid is found to effectively extract antigen in the range of 0.1 M to 1.0 M. Antigen is extracted from the organism for 5 minutes, although a range from instantaneous to 30 minutes is acceptable. The solution is neutralized using 120 µl of a buffer containing 1.5 M MOPSO, pH 7.3, 0.2% TWEEN 20™ detergent, final pH range of 7.0 to 7.5 is desired. (¶ bridging cols. 10-11)

Murray teaches coloring assay reagents with inert colorants such that as each step in a procedure such as an immunoassay is completed, a resultant color change indicates which steps in the procedure have been accomplished.

It would have been obvious to one of ordinary skill in the art to optimize the experimental parameters and reagents of the method of Imrich et al. by selecting such conventional components for generating nitrous acid and times of extraction as described by Bogart et al. Where the general conditions of a claim are disclosed in the prior art, discovering the optimum or workable ranges involves only routine skill. *In re Aller*, 220 F.2d 454, 105 USPQ 233 (CCPA 1955).

Secondly, it would have been further obvious to use inert colorants in one or more reagents of the assay of Imrich et al. which change color upon completion of the reaction in which said one or more reagents are used as a quality control measure to conclusively indicate that method steps of reaction has been accomplished as suggested by Murray.

Traversal and Response

Applicant repeats the above arguments, i.e. Imrich et al. requires devices containing complex housings and does not disclose the the step of contacting the sample receiving region **after** the reaction step, adding that neither Bogart et al. nor Murray corrects the contacting issue. First, the housing argument is not cogent to claims 3 and 5 since the negative housing limitation only appears in claim 7. Second, the rebuttal to both arguments given above is reiterated.

Applicant argues neither Bogart et al. nor Murray are properly combinable with Imrich et al. because Murray does not describe lateral flow assay devices and Bogart et al. requires further manipulation of the extracted reagent to bring it into contact with the test surface. In response, under the law, it is not necessary that any of the references used for rejection provide a "specific suggestion" to make the appropriate modification, nor is it necessary that the motivation to make the modification be the same as that of applicants. The Court of Appeals for the Federal Circuit in *Interconnect Planning Corp.*, 227 USPQ 543 (Fed. Cir. 1985), stated that "Not only must the claimed invention as a whole be evaluated, but so also must the references as a whole, so that their teachings ar applied in the context of their significance to a technician at that time." Id. at 551. Here, Bogart et al., like Imrich et al., is centrally concerned with nitrous acid extraction as a

means of antigen extraction. Murray, like Imrich et al., uses colorants to monitor method steps and to provide for quality control. (In Imrich et al. see e.g. col. 6, lines 35-42, where Imrich et al. uses an assay indicator to show whether the neutralization of extract is complete.) Therefore, this argument is not persuasive.

REMARKS

In conclusion, applicant's amendments and arguments filed June 11, 1998 have been fully considered but are not deemed convincing of patentability for the above reasons and reasons of record.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

The prior art made of record and not relied upon is considered pertinent to applicant's disclosure.

Chan et al. (US 5,177,024) describes a dip-stick immunoassay for determining grain protein wherein the dip-stick coated with a monoclonal antibody against the antigen(s) of interest is dipped into diluted sample extract (see e.g. col. 7, § 2.2).

Maggio (US 4,859,610) describes an immunoassay and incubation device therefore for extracting a soluble analyte from a solid or semisolid sample into a liquid medium, for separating the soluble analyte from the unextracted components of the solid or semisolid sample, and for assaying the soluble analyte, the device comprising (1) a vessel for receiving and containing the solid or semisolid sample and the liquid medium, (2) a means for extracting the soluble analyte from the solid or semisolid sample into the liquid medium, said extraction means removably contained within said vessel, (3) an incubation chamber removably contained within said vessel; (4) said incubation chamber defining one or more aperatures positively immersible within the liquid medium of said vessel, the apertures having a cross sectional area sufficiently large for passing detectable quantities of the soluble analyte and a cross sectional diameter sufficiently small for blocking passage of unextracted components between said vessel and said incubation chamber, and (5) a solid phase assay member coated with a binding immunological reagent inserted within said incubation chamber when assaying the soluble analyte therein.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Carol A. Spiegel whose telephone number is (703) 308-3986.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, James Housel, can be reached on (703) 308-4027. The fax phone number for the organization where this application or proceeding is assigned is (703) 308-4242.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.

Carol A. Spiegel
August 28, 1998

Carol A. Spiegel

CAROL A. SPIEGEL
PRIMARY EXAMINER
GROUP ~~1800~~ 1600